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FLUORINATION OF AROMATIC α-HYDROXYESTERS WITH N,N-DIETHYL-1,1,2,3,3,3-HEXAFLUOROPROPANEAMINE

S. WATANABE, T. FUJITA, M. SAKAMOTO, H. ENDO

Department of Applied Chemistry, Faculty of Engineering, Chiba University, Yayoicho, Chiba 260 (Japan)

and T. KITAZUME

Department of Bioengineering, Tokyo Institute of Technology, Ohokayama, Meguro-ku, Tokyo 152 (Japan)

SUMMARY

The reaction of N,N-diethyl-1,1,2,3,3,3-hexafluoropropaneamine (PPDA) with aromatic α-hydroxyesters exchanged F for OH and gave their corresponding fluorides. For example, ethyl 2-fluoro-2-(p-tolyl) acetate was obtained from the reaction of ethyl 2-hydroxy-2-(p-tolyl) acetate with PPDA.

INTRODUCTION

Fluorinated compounds have been widely utilized in biochemical and industrial investigations. Fluoroalkyl Amino Reagent (FAR) and Diethyl Amino Sulfur Trifluoride (DAST) are useful fluorinating reagents for various alcohols. Recently, we reported that N,N-diethyl-1,1,2,3,3,3-hexafluoropropaneamine (PPDA, Ishikawa reagent) is useful as a fluorinating reagent for nitroalcohols [1]. However, the reactions of various aromatic α-hydroxyesters with PPDA have not been studied in detail. In this paper, the reactivities of aromatic α-hydroxyesters and the chemical structures of the products were studied.

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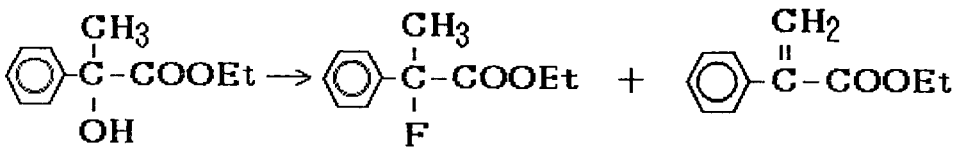
RESULTS

It is known that PPDA is a useful fluorination reagent for saturated primary alcohols [2]. Other authors reported the fluorination of ethyl mandelate [3] and aromatic β-hydroxyesters containing a $PhC(H)(OH)CH(R_1)$-$COOC_2H_5$ group [4]. The present paper describes the reactions of various α-hydroxylated esters containing the group R_1-$PhC(R_2)(OH)COOC_2H_5$ with PPDA to give the corresponding fluorides.

The reaction of α-hydroxyesters related to mandelic ester with PPDA gave their corresponding fluorides in good yields. For example, from the reaction of PPDA with ethyl 2-hydroxy-2-(p-tolyl)acetate (I), ethyl 2-fluoro-2-(p-tolyl) acetate (II) was obtained. Other results are listed in the TABLE 1.

I II

Fluorination of t-butyl alcohol with PPDA gives its fluoride in good yield [3]. However, the reactions of most tertiary alcohols with PPDA give the corresponding fluoride in only low yields. Undesirable side reactions such as dehydration, isomerisation and dimerisation of alcohols give rise to the main products. Interestingly we have found that the reaction of PPDA with aromatic tertiary hydroxyesters gives their corresponding fluorides. For example, from the reaction of PPDA with ethyl 2-hydroxy-2-phenyl propionate (III), ethyl 2-fluoro-2-phenylpropionate (IV) was obtained. However, the dehydrated product, ethyl 2-phenylacrylate (V) was produced as the by-product. The results are listed in TABLE 2.



III IV V

TABLE 1

Fluorination of ethyl 2-hydroxyarylacetate

Compound (A)		Compound (B)[a,b]	
	Yield (%)[c]	^{19}F NMR	
Ar		δ (ppm)	J_{HF}(Hz)
o-Xylyl	73	+107.2	J=41.5
m-Xylyl	66	+112.2	J=41.3
p-Xylyl	55	+ 97.3	J=41.4
p-Ethylphenyl	66	+ 99.5	J=40.5
p-Isopropylphenyl	64	+100.3	J=40.3
p-n-Butylphenyl	66	+101.5	J=40.1
p-Bromophenyl	59	+ 80.1	J=40.8
p-Chlorophenyl	52	+ 83.2	J=40.6
p-Methoxyphenyl	57	+ 93.0	J=41.2
p-Ethoxyphenyl	55	+ 92.0	J=41.0
p-Isopropoxyphenyl	50	+ 91.0	J=41.3

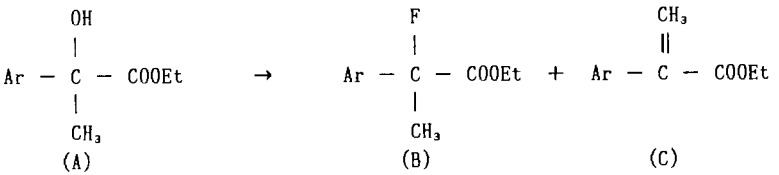
[a] The microanalyses were in satisfactory agreement with the calculated values: C ±0.30%, H ±0.05%

[b] All compounds were separated by liquid chromatography with silica gel column using n-hexane containing 10% ethylacetate as the solvent. All these compounds were liquid.

[c] The yield was calculated as isolated yield.

TABLE 2

Fluorination of ethyl 2-(p-alkylphenyl)-2-hydroxypropionate



Compound (A)	Compound (B)[a,b]		Compound (C)[a,b]
	Yield (%)[c]	^{19}F NMR	Yield (%)[c]
Ar		δ (ppm), J_{HF}(Hz)	
Phenyl	60	+ 72.0(q), J=22.2	15
p-Methylphenyl	60	+ 62.3(q), J=22.3	20
p-Ethylphenyl	55	+ 61.2(q), J=22.1	18
p-iso-Butylphenyl	53	+ 59.8(q), J=22.8	18
p-sec-Butylphenyl	52	+ 59.3(q), J=22.6	15

[a] The microanalyses were in satisfactory agreement with the calculated values: C ±0.30%, H ±0.05%

[b] All compounds were separated by liquid chromatography with silica gel column using n-hexane containing 10% ethylacetate as the solvent. All these compounds were liquid.

[c] The yield was calculated as isolated yield.

EXPERIMENTAL

The reaction products were analyzed by GLC on a Shimadzu Model GC-3BF Chromatograph Apparatus using a 3m×3mm column of 15% Silicone DC 200 on 60~80 mesh Celite 545. ^{1}H NMR and ^{19}F NMR spectra were obtained using $CDCl_3$ as a solvent on a Hitachi Model R-24 spectrometer. IR spectra were obtained on a JASCO Model IR-G infrared spectrophotometer. Hydroxyesters except commercial ones were prepared by the reaction of aromatic aldehyde and bromoform in the presence of potassium hydroxide and lithium chloride [5].

Fluorination of ethyl 2-hydroxy-2-(p-tolyl) acetate (Ⅰ)

A solution of PPDA (2.2g, 10mmol) in CH_2Cl_2(15ml) was added dropwise into a solution of (Ⅰ)(0.8g, 4.1mmol) in CH_2Cl_2(20ml) at room temperature. After stirring for 24hr, the reaction mixture was left overnight. It was poured into water and an oily product was extracted with diisopropylether. The extract was washed with water, dried over anhydrous sodium carbonate, filtered, and evaporated to remove the solvent. The residue was chromatographed on a silica gel column and eluted with n-hexane containing 10% ethylacetate. Elution gave 0.45g of pure ethyl 2-fluoro-2-(p-tolyl) acetate (Ⅱ)(yield 55%). IR(cm^{-1}): 1750; ^1H NMR(δ, ppm)($CDCl_3$): 1.19(3H, t, J=7.2Hz, $-OCH_2\underline{CH_3}$), 2.31(3H, d, J_{HF}= 1.8Hz, $PhC\underline{H_3}$), 4.19(2H, q, J=7.2Hz, $-OC\underline{H_2}CH_3$), 5.71(1H, d, J=48.0Hz, -CHF-), 7.26(4H, ABq, J=8.4Hz, 12.6Hz, aromatic protons); ^{19}F NMR: +97.3(1F, dd, J=48.0 Hz, J=1.7Hz, -CHF-). Other aromatic hydroxyesters were treated with PPDA in the same manner, and the results are listed in TABLE 1.

Fluorination of ethyl 2-hydroxy-2-phenyl propionate (Ⅲ)

A solution of PPDA (2.2g, 10mmol) in CH_2Cl_2(15ml) was added dropwise into a solution of (Ⅲ)(0.78g, 4.0mmol) in CH_2Cl_2(20ml) at room temperature. After stirring 24hr, the reaction mixture was left overnight. It was poured into water and an oily product was extracted with diisopropylether. The extract was washed with water several times, dried over anhydrous sodium carbonate, filtered, and evaporated to remove the solvent. The residue was chromatographed on a silica gel column and eluted with n-hexane containing ethylacetate (10%). The first elution gave 0.47g of pure ethyl 2-fluoro-2-phenylpropionate (Ⅳ)(yield 60%). IR(cm^{-1}): 1740; ^1H NMR(δ, ppm)($CDCl_3$): 1.18(3H, t, J=7.2Hz, $C\underline{H_3}CH_2$-), 1.92(3H, d, J=22.2Hz, $C\underline{H_3}$-$\underset{|}{C}$-F), 4.16(2H, q, J=7.2Hz, $CH_3C\underline{H_2}$-), 7.26~7.65(5H, m, aromatic protons); ^{19}F NMR: +72.0(1F, q, J=22.2Hz, -$\underset{|}{C}$F-). The second elution gave 0.106g of ethyl 2-phenylacrylate (Ⅴ)(yield 15%). IR(cm^{-1}): 1700; ^1H NMR (δ, ppm)($CDCl_3$): 1.27(3H, t, J=7.2Hz, CH_3-), 4.16(2H, q, J=7.2Hz, $-CH_2$-), 5.82 and 6.30(1H×2, each d, each J=0.6Hz, -$\underset{|}{C}$=CH_2), 7.30~7.65(5H, m, aromatic protons) Other aromatic hydroxyl esters were treated with PPDA in the similar manner, and the results are listed in TABLE 2.

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